

Rejection Under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1-5 under 35 U.S.C. § 103(a) as unpatentable over Niewohner, et al., (WO 99/24433) in view of Dale, et al., (Org. Proc. Res. Dev. 4:17-22, 2000) and Knaggs, et al., (Sulfonation and Sulfation, Kirk-Othmer Encyclopedia of Chemical Technology, pages 1-13, 2000) (Paper No. 9, pages 2-5). Applicants respectfully traverse.

The present invention relates to a process for the preparation of sulphonamide-substituted imidazotriazinones. Specifically, an imidazotriazinone is reacted with sulfuric acid, and the product of this reaction is then reacted with thionyl chloride and an amine to yield a sulphonamide-substituted imidazotriazinone.

The process disclosed by the prior art reference, Niewohner, et al., utilizes direct chlorosulfonation by reacting the compound with chlorosulfonic acid followed by a reaction with an amine. As mentioned in the specification of the present invention, this process leads to the production of imidazotriazinonesulphonyl chlorides as intermediates which are sensitive to hydrolysis (*see, e.g.*, page 2, lines 3-6 of the specification). This sensitivity to hydrolysis limits the possibility of conversion of this process to an industrial scale because of the yield variations. Furthermore, as exemplified in the Reaction Schematic prepared by the inventor (enclosed), this process has a yield of only 41% over the two step process.

In the process as claimed in the present invention, the yield variations as a result of the hydrolysis of the intermediate are eliminated. Specifically, the reaction with thionyl chloride and the subsequent reaction with an amine are carried out in a one-pot process which eliminates the need to isolate the hydrolysis-sensitive intermediate (*see, e.g.*, page 2, lines 12-19 to page 3, lines 1-3 of the specification). Thus, the process of the present invention is adaptable to industrial scale-up. Furthermore, as shown in the Reaction Schematic, the process of the present invention produces a 77% yield over three steps. Based on the disclosure of Niewohner, et al., it would not have been obvious to one skilled in the art and one skilled in the art would not have been motivated to perform the three step process of the present invention with the expectation of doubling the yield of product, and furthermore, that this claimed process would be adaptable to industrial scale-up.

Dale, et al., describes a reaction scheme in which the chlorosulphonation reaction occurs at the last stage of the reaction scheme, and this reaction scheme only produces an overall yield of 7.5% (page 17, second column and Scheme 1). Furthermore, Dale et al., describes the difficulties of scaling up chlorosulphonation reactions due to the competing hydrolysis, and chlorosulphonation late in the synthesis results in yield losses of the more expensive intermediate (page 17, second column). Thus, according to Dale, et al., "...this route was suboptimal as a commercial manufacturing route..." (page 17, second column). For commercial development, Dale, et al., describes a reaction scheme where the

chlorosulphonation step occurs earlier in the chemical synthesis, specifically prior to cyclization, and thus minimizing the loss of the more expensive intermediate (pages 18 and 19, and Figure 1).

Therefore, based on the disclosure of Dale, et al., it would not have been obvious to one skilled in the art and one skilled in the art would not have been motivated to perform the process of the present invention with the expectation of developing a commercial viable industrial scale-up and in addition, improving the yield of product. In fact, Dale, et al., teaches away from the process of the present invention. Specifically, Dale, et al., states that chlorosulphonation late in the synthesis results in yield losses of the more expensive intermediate. Thus, based on the disclosure of Dale, et al., one skilled in the art would not have been motivated to develop the commercial process of the present invention where the chlorosulphonation still occurs at the later stages of chemical synthesis. Furthermore the yield of the present invention is significantly greater (77%) as compared to the medicinal process (7.5%) described by Dale, et al., where the chlorosulphonation occurs at the later stages of development.

Knaggs, et al., provides a general overview of sulfonation, sulfation, and possible reagents. However, Knaggs, et al., does not teach or suggest the chlorosulphonation process of the present invention. As stated by Dale, et al., "The difficulties of scaling up chlorosulphonation reactions are well-known in chemical development..." (Dale, et al., page 17, column 2). Thus, the overview provided by Knaggs, et al., certainly does not provide the motivation to develop the process of the present invention nor the expectation of developing a process that is commercially viable.

Therefore, one of ordinary skill in the art would not have been motivated at the time of the invention to combine the teachings of Niewohner, et al., Dale, et al., and Knaggs, et al., to develop the process of the present invention, that is, a commercially feasible scale up chlorosulphonation process.

It is therefore respectfully submitted that Niewohner, et al., either singly or in combination with Dale, et al., and Knaggs, et al., fail to teach or suggest the process as presently claimed, and that the current invention is novel and nonobvious in view of the prior art references. For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

For the foregoing reasons, Applicants submit that the claims are in condition for allowance and Applicants respectfully request reexamination of the present application and reconsideration and withdrawal of the present rejections. Should there be any further matter requiring consideration, Examiner Balasubramanian is invited to contact the undersigned counsel.

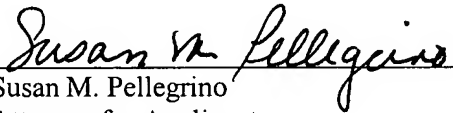
If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 13-3372. If a fee is required for an extension of time not

accounted for, such an extension is requested and the fee should also be charged to undersigned's deposit account. Please note the deadline for response to this Office Action was Sunday, January 11, 2004; and a response was filed on the next business day, January 12, 2004.

Respectfully submitted,

Date: January 12, 2004

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Telephone: (203) 812-6450
Facsimile: (203) 812-6459



Susan M. Pellegrino
Attorney for Applicants
Reg. No. 48,972

REACTION SCHEMATIC

Chlorosulfonation (prior art patent)	Method of the present invention
<p>500 g Imidazotriazinon ↓ ClSO₃H ↓ Sulfotriazinon ↓ N-Ethylpiperazin ↓ 321 g ⇒ 41% yield (over 2 steps)</p>	<p>45 kg Imidazotriazinon ↓ H₂SO₄ ↓ 48.1 kg Sulfotriazinic acid ⇒ 85% Ausb. 22.5 kg ↓ 1.) SOCl₂ 2.) N-Ethylpiperazin ↓ 26.1 kg (91% yield) ⇒ 77% yield (over 3 steps)</p>

